REMARKS/ARGUMENTS

Claims 1 and 6 have been amended to recite that the oral calcium is in the form of a capsule or tablet. Support for this amendment can be found throughout the specification including, for example, page 6, line 35-37.

Claim 6 has been amended to recite "administering by injection . . . about 2 to about 3 g of calcium and at about 2 to about 3 g of magnesium . . . ." Claim 13 has been amended to recite that the "calcium administered by the oral route is administered a dose of about 1 to about 2 g/day." Support for these amendments can be found throughout the specification including, for example, page 6, lines 10-15.

Applicants submit that no new matter has been added via these amendments to the claims.

Interview Summary

Examiners Klinkel and Mehta are thanked for the courtesies extended during telephonic interview conducted with the undersigned on June 24, 2010. In the interview, amendments to overcome the outstanding rejection under 35 U.S.C. § 103 were discussed. Amendments in accordance with the discussion are presented above. In view of the amendments, Applicants submit that all of the outstanding rejections have been met and respectfully request withdrawal of the rejections.

35 U.S.C. § 112, First Paragraph

Claims 6, 11, and 13-14 have been rejected under § 112, first paragraph, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time that the application was filed, had possession of the

claimed invention. (Paper No. 20100323 at 3.) The Examiner has alleged that there is no support in the specification for the recitation in claims 6 and 13 of "at least 1 g calcium," "at least 1 g of magnesium," and "at least 1 g/day." (*Id.*)

Claim 6 has been amended to recite "administering by injection . . . about 2 to about 3 g of calcium and at about 2 to about 3 g of magnesium . . . ." Claim 13 has been amended to recite that the "calcium administered by the oral route is administered a dose of about 1 to about 2 g/day."

Accordingly, the rejection has been rendered moot and withdrawal is respectfully requested.

Moreover, the specification clearly provides support for the recited phrases. In particular, the specification teaches:

> The concentrations of calcium and magnesium salts are chosen so as to allow **intravenous administration of 2 to 3 g/day of said salts during the administration of oxaliplatin**. The calcium concentrations are chosen so as to allow **administration of 1 to 2 g/day per os during the eight days which follow**.

(P.6, ll.10-15 (emphasis added).) Accordingly, the specification provides explicit support for the claims as amended.

In view of the foregoing, one skilled in the relevant art would readily have recognized that the Applicants were, at the time that the application was filed, in possession of the claimed invention. Accordingly, Applicants submit that the claims, as amended, fully comply with all of the requirements of 35 U.S.C. § 112.

35 U.S.C. § 103

Claim 1 has been rejected under 35 U.S.C. § 103(a) as unpatentable over *Lainé-Cessac* in view of Chazard, U.S. Patent Application 2002/0045632 ("*Chazard*"). (Paper No. 20100323 at 5.)

In making the rejection, the Examiner has alleged that *Lainé-Cessac* teaches that "the anticancer agent oxaliplatin induces neurotoxicity (1st sentence). This neurotoxicity can be dramatically improved by immediately treating patients undergoing oxaliplatin treatment with intravenous calcium gluconate (1 g) and magnesium sulfate (1 g)." (*Id.*) The Examiner has acknowledged that *Lainé-Cessac* does not teach that the injectable calcium and calcium in the oral form are separate compositions. (*Id.* at 6.)

The Patent Office has relied on *Chazard* as disclosing "the use of an oral formulation of calcium folinate to potentiate the coadministration of oxaliplatin in order to treat tumors (abstract, paragraph 36)." (*Id.*) The Patent Office then determined that "[i]t would have been obvious . . . to assemble a kit containing oxaliplatin, injectable calcium, injectable magnesium and calcium in the oral form where the two calcium compositions are separate compositions . . . ." (*Id.* at 7.)

Lainé-Cessac discloses that the acute neurotoxic effects of oxaliplatin administration can be dramatically improved by intravenous administration of calcium gluconate and magnesium sulfate immediately after onset of the neurotoxic effects. *Lainé-Cessac* is silent as to oral administration of calcium.

Chazard discloses "[o]ral dosage form for administration of the combination of tegafur, uracil, folinic acid, and oxaliplatin and method of using the same." (Title (emphasis added).) In fact, *Chazard* is directed specifically to an oral dosage as an improvement upon an injectable form of its compositions:

> It has been observed that 5-fluorouracil can enhance the activity of oxaliplatin. However, because 5-fluorouracil cannot be administered orally, the mode of administration for this combination therapy requires a more invasive form of administration such as by intravenous injection, and

> therefore typically requires administration by trained medical personnel.
>
> ***It would be an advance*** in the art of treating tumors, especially colorectal cancerous tumors, ***if a therapy could be developed employing a potentiated form of oxaliplatin through the action of 5-fluorouracil in a convenient dosage form for oral administration***.

(¶¶ 0007-0008 (emphasis added).)

Chazard discloses that "5-fluorouracil cannot be administered orally." (¶ 0003.) *Chazard* discloses, however, that "the combination of tegafur and uracil in amounts sufficient to convert tegafur to 5-fluorouracil (preferably a molar ratio of about 1:4) can be administered orally. It was unexpectedly discovered that oral administration of this combination produced sufficient 5-fluorouracil that potentiation of oxaliplatin would take place despite the inability of 5-fluorouracil itself to be effectively administered orally." (¶ 0015.) In sum, *Chazard* explicitly discloses that oral administration of its compounds is absolutely critical to the invention:

> The ***oral dosage form*** used in the present invention ***provides significant advantages*** over administering the combination by other modes of administration which are more invasive. In the treatment of tumors, a potential ***reduction in the cost of therapy*** because skilled medical personnel are not required to administer the drug and the ***psychological benefits afforded a patient*** by taking an oral medication provide significant benefits for patient care.

(¶ 0016 (emphasis).)

Claim 1 recites injectable calcium and injectable magnesium. Thus, any combination of *Lainé-Cessac* and *Chazard* that results in the claimed method must necessarily include the an injectable form of magnesium and calcium. However, a method using the claimed kit would destroy the operability of *Chazard*. Simply

put, a method requiring an injection would 1) increase the cost of therapy and 2) remove the psychological benefits afforded a patient by taking an oral medication. Both of which are stated objects of the invention of *Chazard*.

However, a modification of references that destroys the operability of the references is not obvious. *See*, *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (reversing the decision of obviousness on the ground that the proposed modification of the prior art would have rendered the claimed invention inoperable for its intended purpose). For this reason, the rejection fails to present a *prima facie* case for obviousness and withdrawal is requested.

As discussed in the Applicants' previous responses, the claimed invention is also nonobvious because it solves a problem that the prior art did not recognize. This argument stands unrebutted by the present Office Action and is re-presented here for completeness.

Before the present Applicants' invention, it was believed that the neurotoxic effects of oxaliplatin appeared only during or immediately after infusion of the oxaliplatin. In other words, the late-onset of neurotoxic effects was not a concern. Consequently, and as borne out by the cited prior art itself, therapies for treating these neurotoxic effects focused exclusively on immediate treatment. *See, e.g., Lainé-Cessac*. However, this belief turned out to be mistaken. As Applicants explained in paragraph [0053] of the present specification, "[i]n some cases, it is found necessary to continue with the administration of Ca in order to reduce the risk of ***onset of neurological manifestations at a distance from the administration of oxaliplatin***." (Emphasis added.) In solving this problem with a combination of injectable

and oral administration of calcium, Applicants' claimed invention thus produces unexpected results in treating the previously unappreciated late-onset neurological side effects of oxaliplatin.

Inventions based on application of known solutions to previously unknown problems have been held to be non-obvious and patentable. In *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923), the Supreme Court ruled that the first recognition of the existence of a problem is not obvious and involves discovery and invention. In *Eibel Process*, the patent in question was directed to an improvement in a standard paper making machine. In the machine, a stream of pulp stock flowed onto a moving wire cloth in order to drain water out of the stock over the 30 foot-length of the cloth. The prior art taught that increasing the speed of the wire cloth increased productivity, but at the same time, caused the defective paper with poor quality. The patentee's contribution was to increase the pitch of the wire cloth in order to use gravity to increase the rate of flow of pulp on the wire cloth to equal the rate of flow of the wire cloth itself. The Supreme Court held thusly:

> It was the discovery of the source not before known and application of the remedy for which *Eibel* was entitled to be rewarded in his Patent. . . . We cannot agree with the Circuit Court of Appeals that the causal connection between the unequal speeds of the stock and the wire, and the disturbance and rippling of the stock, and between the latter and the defective quality of the paper in high speeds of the machine was so obvious that perception of it did not involve discovery which will support a patent.

Eibel Process, at 68.

Similarly, in *In re Nomiya*, 509 F.2d 566, 184 USPQ 607 (C.C.P.A. 1975), the Court of Customs and Patent Appeals (CCPA)

held that the doctrine established by the Supreme Court in *Eibel Process* also applies when the inventor was the first to encounter or perceive a problem even though he uses known or obvious means of solving it. *Nomiya* dealt with an improvement in an insulated gate-type field effect transistor (IGFET) for use as a switching device in memory circuits having very low capacitance. The CCPA reasoned thusly:

> If, as appellants claim, there is no evidence of record that a person of ordinary skill in the art at the time of appellants' invention would have expected the problem in the IGFET to exist at all, it is not proper to conclude that the invention which solves this problem, which is claimed as an improvement of the device, would have been obvious to that hypothetical person of ordinary skill in the art. The significance of evidence that a problem was known in the art is, of course, that knowledge of a problem provides a reason or motivation for workers in the art to apply their skill to its solution. Logically, the instant situation is one step removed from the circumstances illustrated by *Eibel Process Co. v. Minnesota & Ontario Paper Co.* … where *the problem* of rippling in paper produced on Fourdrinier paper-making machines at high speed *was known*, but the source of the problem was not.

Nomiya, 509 F.2d at 572, 184 USPQ at 612-613.

For this additional reason, the rejection fails to present a *prima facie* case for obviousness. Accordingly, for all of the foregoing reasons, the reconsideration and withdrawal of the rejection are requested.

Claims 1, 4-6, and 11-14 have been rejected under 35 U.S.C. § 103(a) as unpatentable over *Lainé-Cessac* in view of Grolleau *et al.*, *A Possible Explanation of a Neurotoxic Effect of the Anticancer Agent Oxaliplatin in Neuronal Voltage-Gated Sodium*

Channels, J Neurophysiology 85(5):2293-97 (2001) ("*Grolleau*") and Mazer *et al.*, U.S. Patent 5,698,222 ("*Mazer*"). (Paper No. 20100323 at 7-8.) In making the rejection, the Examiner has relied on the previous characterization of *Lainé-Cessac*. (*Id.* at 8.) The Examiner has acknowledged that *Lainé-Cessac* does not teach injectable and oral calcium as separate compositions or the administration of oral calcium following treatment with oxaliplatin. (*Id.*) The Examiner has alleged that *Grolleau* teaches "administration of Ca and Mg ions act to prevent acute neurotoxic side effects of oxaliplatin treatment (abstract)." (*Id.*) The Examiner has alleged that *Mazer* teaches that calcium is an essential nutrient and that old age and oxalic acid act to inhibit calcium absorption and that calcium may be taken orally as a supplement. (*Id.* at 8-9.) The Examiner concluded that the claimed invention was obvious over the combined references. Applicants respectfully traverse the rejection.

As noted above, with regard to the rejection of claim 1, *Lainé-Cessac* teaches only intravenous administration of calcium and magnesium. Thus, *Lainé-Cessac*, at best, teaches a single injectable form of calcium. *Lainé-Cessac* does not teach two different forms of calcium. Nor does it teach any calcium in oral administration form.

Grolleau teaches only that administration of calcium and magnesium by infusion before and after treatment with oxaliplatin can reduce neurotoxic effects:

> In fact, our electrophysiology results are consistent with previous clinical observations (Lainé-Cessac), and immediate oxalate control could be expected to prevent some of the neurological effects observed during and after oxaliplatin treatment. **When Ca2+ and Mg2+ were infused to patients** before and after oxaliplatin administration, oxaliplatin-induced acute neurotoxicity was highly reduced . . . .

P.2297 (emphasis added). Thus, even combined *Lainé-Cessac* and *Grolleau* teach only infusion of calcium and magnesium. They teach absolutely nothing about oral calcium.

Mazer is directed exclusively to a oral calcium supplement to improve calcium absorption. It notes numerous inhibitors of calcium absorption, including oxalic acid, but only if achlorhydria (absence of gastric acid) is present. (Col.3, l.54 – col.4, l. 14 (Table 2).) *Mazer* is completely silent as to neurotoxicity of any type, much less any caused by oxaliplatin administration. *Mazer* is completely silent as to any injectable calcium or infusion thereof. *Mazer* teaches that oral calcium absorption can be increased certain calcium salts are injected orally in conjunction with vitamin D in a low pH composition or with an , *e.g.*, ascorbic acid.

In fact, all that the Examiner relies on *Mazer* as teaching is that calcium is an essential nutrient and that it should be ingested daily. In sum, *Lainé-Cessac* and *Grolleau* teach the administration of calcium by infusion for a particular use, and *Mazer* teaches oral ingestion of calcium for another, completely different use. None of the references teach that there is any advantage to the combined use of oral and infused calcium. In fact, *Lainé-Cessac* and *Grolleau* make clear that infusion is the only route of delivery they contemplate. Likewise, *Mazer* is explicitly confined to the consideration of oral ingestion of calcium.

In short, there is nothing in any of the cited reference that would provide a rationale for one of routine skill in the art to do as the Applicants have done and combine oxaliplatin, with injectable calcium and magnesium, and oral calcium in a kit, or a method employing these components as claimed.

The routineer in the art, however, is an objective legal construct, who is presumed to think along conventional lines, without undertaking to innovate, whether by systematic research or by extraordinary insights. *See Life Technologies Inc. v. Clontech Lab, Inc.*, 224 F.3d 1320, 1325, 56 U.S.P.Q.2d 1186, 1190 (Fed. Cir. 2000) (*quoting Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). Moreover, prior art publications must be evaluated in their entirety. It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *See*, *In re Mercer* 515, F.2d 1161, 1165-66, 185 U.S.P.Q. 774, 778 (C.C.P.A. 1975).

When the cited references are considered in their entirety, one of skill in the art would not have been provided with any rationale to do as the Applicants have done. In sum, one of skill in the art armed with *Lainé-Cessac*, *Grolleau*, and *Mazer* can arrive at the claimed kits and methods only through the exercise of impermissible hindsight reconstruction. Accordingly, the cited references are insufficient to support a *prima facie* case for the obviousness of the claims. Withdrawal of the rejection is respectfully requested.

As discussed in the Applicants' previous responses and above, the claimed invention is also nonobvious because it solves a problem that the prior art did not recognize. This argument stands unrebutted by the present Office Action and is re-presented here for completeness.

Before the present Applicants' invention, it was believed that the neurotoxic effects of oxaliplatin appeared only during or

immediately after infusion of the oxaliplatin. In other words, the late-onset of neurotoxic effects was not a concern. Consequently, and as borne out by the cited prior art itself, therapies for treating these neurotoxic effects focused exclusively on immediate treatment. *See, e.g., Lainé-Cessac; Grolleau.*

However, this belief turned out to be mistaken. As Applicants explained in paragraph [0053] of the present specification, "[i]n some cases, it is found necessary to continue with the administration of Ca in order to reduce the risk of ***onset of neurological manifestations at a distance from the administration of oxaliplatin***." (Emphasis added.) In solving this problem with a combination of injectable and oral administration of calcium, Applicants' claimed invention thus produces unexpected results in treating the previously unappreciated late-onset neurological side effects of oxaliplatin.

As previously discussed, inventions based on application of known solutions to previously unknown problems have been held to be non-obvious and patentable. *See e.g., Eibel Process Co.*, 261 U.S. at 68.45 (1923); *In re Nomiya*, 509 F.2d at 572. For this additional reason, the rejection fails to present a *prima facie* case for obviousness. Accordingly, for all of the foregoing reasons, the reconsideration and withdrawal of the rejection are requested.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully

requested that she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which she might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: September 29, 2010

Respectfully submitted,
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